CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DINOCAP

Chemical Code #00344, Tolerance #00341
SB 950-214

July 18, 1986
9/14/87; 9/28/90

I. DATA GAP STATUS

Combined, Rat:	Data gap, inadequate study on file, no adverse effect indicated.
Chronic Toxicity, Rat:	Data gap, inadequate study on file, no adverse effect indicated.
Chronic Toxicity, Dog:	No data gap, possible adverse effects.
Oncogenicity, Mouse:	Data gap, inadequate study on file, possible adverse effect indicated.
Reproduction, Rat:	Data gap, inadequate study on file, no adverse effect indicated.
Teratology, Rat:	Data gap, inadequate study on file, no adverse effect indicated.
Teratology, Rabbit:	No data gap, possible adverse effect.
Teratology, Mouse:	Inadequate studies, possible adverse effect indicated
Gene Mutation:	No data gap, possible adverse effect.
Chromosome Effects:	No data gap, no adverse effect.
DNA Damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates a possible adverse effect
File name: T900928
1987 version by Gee, revised by G. Chernoff, 9/28/90

II. TOXICOLOGY SUMMARY

Cross-reference data
(Test type 619) 029 050471 "Accountability Study for Karathane Technical". (Rohm and Haas, 4/2/85, No.85-72) Composition of several lots of Karathane Technical produced by the same process as in previous years. HGM, 9/14/87 and Gee, 9/14/87.
NOTE: This report can be cross-referenced to any study for which purity/composition is not included.

COMBINED, RAT

021 037793, "Chronic Toxicity Study for 30 Months with Karathane in Rats", (Inst. Env. Tox., 3/12/1980). Dinocap, lots 2-0375, TD 76-91, 92, composition given as 76.4% crotonates, 1.1% dinitrooctyl-phenols with the remainder not identified. Fed in the diet to 80/sex/group of Wistar SPF-JCL rats at 0, 20, 200 or 2000 ppm for 130 weeks; tentative NOEL = 200 ppm; Eight/sex/group were sacrificed at 13, 26 and 52 weeks so total available at term was 56/sex/group. Based on body weight, 2000 ppm was considered adequate for the high dose. **UNACCEPTABLE**, not upgradeable (no analysis of diet; no inventory of actual tissues examined; housed 5/cage so no individual food consumption). **NO ADVERSE EFFECT REPORTED** other than mortality and decreased weight gain at the high dose. Rebuttal in 341-029 indicates additional tabulations of data should be available within 6 months of 11/25/86. JR(G), 12/30/85 and 7/20/87.
EPA 1-liner: Supplementary with no conclusions until requested data have been received and reviewed (dated 7/9/85).

006 024868, Abstract of Record #037793. JR(G), 12/30/85.

CHRONIC TOXICITY, RAT

006 024877, "Acute and Chronic Toxicity Studies on 2,4-Dinitro-6-(1-Methylheptyl) phenyl crotonate (Karathane): Effect of Adding Karathane to the Diet of Rats", (Medical College of Virginia, 5/59, Publ. in Arch. int. Pharmacodyn. 119: 31-42 (1959). Dinocap, technical (see 050471 in 029). Fed at 0, 10, 50, 250, 500 or 1000 ppm in the diet for 2 years; **NO ADVERSE EFFECT REPORTED** other than mortality. Insufficient information for independent evaluation. Apparent NOEL from body weight is 500 ppm. **UNACCEPTABLE** (histopathology on major organs only, no data presented, too few animals (10/sex); no dose justification; no dosing analysis. JR(G), 6/7/85.
EPA 1-liner: no grade; systemic NOEL = 500 ppm (decreased weight gain).

006 024874, Brief review of toxic effects of Nitro compounds and related phenolic pesticides. JR(G), 6/7/85.

CHRONIC TOXICITY, DOG

****020 37792**, "104-Week Toxicity Study in Dogs--Karathane Technical", (also, abstract Vol.006 #24869); (Hazleton Labs., 8/6/1979). Dinocap, 78%, was fed to Beagle dogs at doses of 0, 15, 60 and 240/120/180 ppm; 107 week exposure; 4/sex/group; this study had a second review by F. Martz (3/27/86). NOEL = 15 ppm (0.4 mg/kg/day). High dose was adjusted because of anorexia, weight loss and mortality. Animals were sacrificed in week 62. **ADVERSE EFFECTS**, eyes (retinal atrophy, reduced vascularization) and heart effects (EKG indicative of myocardial damage (ischemia or fibrosis) and/or hypertrophy, ventricular dilation seen grossly. Retinal atrophy seen ophthalmoscopically and microscopically in mid (7/8) and high dose (4/4) dogs. Mortality: 4/8 in high dose group. Data on EKGs are being tabulated by Rohm and Haas, and will be submitted to CDFA to assist in evaluation of the adverse effect. Initially evaluated as unacceptable by J. Gee (12/30/85),

upgraded to **ACCEPTABLE** with submission of Document #341-029, Record #050473, analysis of diet, Record #050474, individual gross necropsy findings, and Record # 50471, composition of test material. JG, 12/30/85; HGM, 7/21/87 and Gee, 7/21/87.
EPA 1-liner: Minimum. Systemic NOEL = 15 ppm. Systemic LEL = 60 ppm. (histologic retinal atrophy) (no effect on hepatic oxidative phosphorylation at levels of 15 and 60 ppm--only levels tested.) Levels tested in beagles--0, 15, and 60 ppm.

029 050473 and 050474, "Analysis of Toxicology Feed Samples from Study 417-358 (RAR77-0292)", and "Individual Animal Data on Gross Necropsy" addenda to "Karathane:Two Year Dog Toxicity Study--Final Report". HGM, 7/21/87
and Gee, 7/21/87.

006 024869, Abstract of 020 37792 above. JR(G), 6/7/85.

006 024878, "Acute and Chronic Toxicity Studies on 2,4-Dinitro-6-(1-Methylheptyl) Phenyl Crotonate (Karathane): One Year Feeding Study in Dogs." (1959, Medical College of Virginia). Published in Arch. int. Pharmacodyn. 119: 31-42 (1959). Dinocap, no purity stated (see 050471 in 029); fed to mongrel dogs, 3/group (no sex given) at 0, 10, 50, 100, 250 and 1000 ppm for up to 1 year. The last two were lethal. **UNACCEPTABLE** (limited histopathology on all animals). Systemic NOEL = 50 ppm. Weight loss at 100 ppm and lethality at 250 and 1000 ppm with liver necrosis and other findings. JR(G), 6/7/85
EPA 1-liner: no grade; systemic NOEL = 50 ppm (liver cell necrosis and mortality at 250 ppm, depressed body weight gain).

ONCOGENICITY, RAT

See combined rat

ONCOGENICITY, MOUSE

022 037795, "Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Vol. I. Carcinogenic Study", (Bionetics, 8/1968). Over 20,000 mice used in 18 month studies with 130 pesticides; Karathane, 78%, given as a single subcutaneous dose at 10 mg/kg or an oral dose of 1.0 mg/kg, 18/sex/group; **UNACCEPTABLE** (protocol varies widely from guidelines. **ADVERSE EFFECTS** reported: (reticulum cell carcinoma). The data are presented in table form and are illegible, thus making use of the study for risk assessment impossible. JR(G), 12/30/85.

022 037794, "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", (1969, publ. in Journal of the National Cancer Institute 42: 1101 (1969), Innes, J. M. et al.). Brief summary of onco mouse study fed 3 ppm for 80 weeks. Insufficient information for evaluation.

006 24880, No data, no source. JR(G), 6/7/85.

REPRODUCTION, RAT

002 001538, "Karathane: A Three Generation Reproduction Study in Rats", (Hazleton, 7/1/1976, Report No. 417-352, Rohm and Haas No 76RC-1064). Dinocap, 82% (see 050471). Protocol: 10 males were fed Dinocap for 9 weeks, then rotated weekly over 3 weeks with 2 females each, 3

generations with 1 litter per generation for repro study. Second litters from the P_2 and P_3 used for teratology. Histopathology on 10/sex/group of F_3a with none for F_0. Dose levels 0, 2, 20, 200 ppm in diet. NOEL >200 ppm (10 mg/kg/day). Slight effect on F2b generation noted at 200 ppm in terms of reduced viability and increased resorptions -- report states the values are within the labs' experience. Parameters with theF_3 litters were comparable to controls. **UNACCEPTABLE**, not upgradeable (no diet analysis, no homogeneity data, no F_0 histopathology data provided, inadequate high dose (MTD not reached)). JR(G), 6/7/85.
EPA 1-liner: Supplementary. Apparent reproductive effects at 200 ppm as evidenced by decreased pregnancy in rats in the Fb litters.

023 037796, Duplicate of 1538 with addition of ophthalmoscopic exam (1 page). JR(G), 12/30/85.

006 024870, 024881, 024882, Very brief summaries of reproduction study.

009 024846, Rohm & Haas response to EPA Notice of Special Review, 1/9/85.

015 024860, Rohm & Haas response to EPA Notice of Special Review, not identical to 024846 but same discussion presented.

029 050472, "Studies on Dinocap Toxicity. Part V. Preliminary Studies on Effects on Reproduction." (1979,publ.in Bromatologia iChemiaToksykologiczna 12(4):351-356.) (Rebuttal submission by Rohm and Haas.) Dinocap purity not stated (see 050471), F0 rats (10 animals/sex/group), fed at 0 and 5% Dinocap in diet; F1-F3 rats(10 animals/sex/group), fed at 0 and 10 % Dinocap in diet. **NO ADVERSE EFFECT** on reproduction; nominal parental NOEL > 5% of LD_{50} but < 10% (decreased weight gain). Food intake was also reduced for all rats receiving dietary Dinocap, except in the F2 generation. **UNACCEPTABLE** (one dose level per generation in addition to controls; report does not contain supporting data, including raw data, necropsy and histopathology data, and analyses of diets). HGM, 6/15/87 and Gee, 7/16/87.

TERATOLOGY, RAT

023 037796, (Hazleton, 1976). This is a teratology segment to Record# 1538, reproduction study. Twenty females/group were C-sectioned at day 19 of gestation of the second litter in the P2 and P3 generations. **NO ADVERSE EFFECTS REPORTED. UNACCEPTABLE**, not upgradeable (MTD not reached - NOEL $\geq$ 200 ppm). JR(G), 12/30/85.
EPA 1-liner: Supplementary; teratogenic NOEL > 200 ppm (HDT); fetotoxic NOEL not determined pending submission of individual fetal skeletal variation data. Maternal NOEL > 200 ppm.

TERATOLOGY, RABBIT

001 001535, "Teratology Study of Karathane in the Rabbit" (Rohm and Haas, 1/16/1984, 83R-022). Dinocap technical, 84%. New Zealand White Rabbit, oral gavage, days 7-19. **UNACCEPTABLE**, all doses too high (0, 3, 12, 48, 64 mg/kg). **POSSIBLE ADVERSE EFFECT**, fetotoxicity and terata (mainly neural tube) were noted at all dose levels, maternal toxicity (abortion, decreased weight gain at 48 and 64, increased incidence of clinical signs noted by lab at 12 and above). (JAP considers maternal toxicity minimal at 12). Maternal NOEL = 3 mg/kg/day. Developmental NOEL< 3 mg/kg/day. JR(G), 6/7/85.
EPA one-liner: Maternal NOEL = 3 mg/kg; Terata NOEL < 3 mg/kg (defects of neural tube, spine and skull). Supplementary.

005 024865, Amended pages to 001535.

001 001536, "Karathane: Oral Range-Finding Study in the Rabbit." (Rohm and Haas, 1984). Range-finding study for #001535.

006 024871, Very brief abstract of 001536.

006 024872, Very brief abstract of 001535.

009 024850, Rohm & Haas comments (on first oral study) to EPA Notice of Special Review 1-9-85.

003 001539, "Teratology Study with Karathane in Rabbits", (Rohm and Haas, 1984, 83R-113). Dinocap technical, 87.8%. Doses of 0.1, 0.5 and 48 mg/kg by gavage on days 7-19 of gestation to New Zealand white rabbits, 40 in control, 48 in low and mid dose groups and 24 in the high dose group. Dosing samples were analyzed by TLC. This study was done to establish a developmental NOEL. Maternal toxicity was seen at 48 mg (decreased weight gain and abortion), maternal NOEL = 0.5 mg/kg. Developmental toxicity was seen at 48 mg/kg (Increased resorptions), NOEL = 0.5 mg/kg/day. Prior review had noted an adverse effect in the reproductive area based on abortion, reduced viability and gestation indices. Second review, JAP 6-9-86, concludes that this is not an adverse effect as maternal and developmental effects occurred at the same dose level, 48 mg/kg, which was clearly an MTD. All fetuses were subjected to visceral and skeletal examination. Four deaths were due to gavage error and 9/23 had abortions at the high dose. **NO ADVERSE EFFECT. ACCEPTABLE. JR(G), 6/7/85 and Parker, 6/9/86.
EPA one-liner: Joint consideration with 1535, Minimum, Maternal NOEL = 3 mg/kg; Terata NOEL = 0.5 mg/kg, neural tube, skull and spinal malformations.

001 001534, (Rohm and Haas, no date). This is a draft report, final report is Vol. 003 # 1539. JR(G), 6/6/85.

006 024873, Very brief abstract of 1539.

009 024849, Rohm & Haas Comments on (second oral rabbit study) to EPA Special Review, 1-9-85.

011 024852, "Range-finding Dermal Teratology Study with Karathane Formulations in Rabbits", (Rohm and Haas, 1985, 84R-248). Range-finding Dermal Teratology Study with Karathane Formulations and technical material in New Zealand White Rabbits. Technical Dinocap, 87.8%, wettable powder, 20.4% and liquid concentrate at 39.8% tested separately. Dermal dose levels of 20, 50, 100 and 200 mg/kg/day, 7/group. **NO ADVERSE EFFECT.** Prior review, JR(G) 6-10-85, indicated an adverse effect in the area of reproductive toxicity. Second review, JAP 6-9-86, concludes that this should not be considered an adverse effect as this is a pilot study and the object is to determine an MTD
and toxicity seen should not be considered a possible adverse effect. JR(G), 6/10/85 and Parker, 6/9/86.
EPA 1-liner: Supplementary. Dermal irritation at all doses; fetotoxic NOEL= 50 mg/kg/day. Maternal NOEL<200mg/kg (technical).

004 008672, Protocol for dermal range finding in rabbits.

009 024848, Rohm & Haas Comments (Dermal range finding) to EPA Special Review, 1-9-85.

018 035827, Duplicate of 024852.

024 037797, Duplicate of 024852.

011 024853, "Dermal Teratology Study with Karathane Technical in Rabbits", (Rohm and Haas, 1985). NZW rabbit dermal teratology, Karathane technical, Lot no. 2410, 87.8% purity. Applied at 0, 25, 50, and 100 mg/kg/day on days 7-19 of gestation. Karathane left on backs for 6 hr/day, then washed off with absolute ethanol; 7 different areas were used to decrease skin irritation. Animals were collared. Maternal NOEL (weight gain decreased) = 50 mg/kg/day. Dermal irritation at all dose levels. Developmental NOEL > 100 mg/kg/day. **ACCEPTABLE. NO ADVERSE EFFECT. JR(G), 12/31/85 and Parker, 6/10/86.
EPA one-liner (7-9-85): Minimum, Maternal NOEL < 25 mg/kg/day (Dermal irritation). Fetotoxic NOEL = 50 mg/kg/day (decreased fetal weight and increased fetal and litter incidences of "skull, bone islands". Teratogenic NOEL > 100 mg/kg/day.

009 024847, Rohm & Haas comments (on rabbit dermal teratology) to EPA Special Review, 1-9-85.

018 035828, Duplicate of 24853

018 035829 Comments on 24853 by E.M. Johnson, Chairman, Anatomy Dept., Thomas Jefferson University. Concludes Maternal NOEL = 50 mg/kg/day and developmental NOEL > 100 mg/kg/day. Dermal irritation at all levels. JR(G), 12/30/85.

024 037798, Duplicate of 24853. JR(G), 12/31/85.

004 008675, Protocol for rabbit dermal teratology, dated 8-84.

005 024866, Protocol for rabbit dermal teratology, dated 1-85.

040 071177, "A Developmental Toxicity Study of Karathane Fungicide/Miticide (Technical) Administered via Stomach Tube to New Zealand White Rabbits", (Hoberman, A.M., Argus Research Laboratories, I.D. No. 018-012, 5/15/87). Karathane Fungicide/Miticide (Lot #R-34914-1), 95.4%, was administered by oral gavage to groups of 20 artificially inseminated Hra New Zealand White Rabbits at dose levels of 0 (1% tragacanth gum vehicle control), 3, 12, 48 or 84 mg/kg/day on days 7-19 of gestation. At 48 and 84 mg/kg/day, maternal toxicity was demonstrated by an increase in abortions and gastric ulceration. At 12, 48 and 84 mg/kg, both maternal weight gain and food consumption were depressed. Developmental toxicity was noted at 48 and 84 mg/kg by the presence of increased resorptions, decreased fetal weights and skeletal ossification, and increased malformations (vertebral asymmetry). Maternal NOEL = 3 mg/kg/day (decreased weight gain and food consumption); Developmental NOEL = 12 mg/kg/day (increased resorptions and malformations, and decreased fetal weights). Since the fetal effects occur at doses eliciting clear signs of maternal toxicity, there is no adverse developmental health effect indicated. The study is **UNACCEPTABLE**, but upgradeable with the submission and favorable review of analyses of the dosing solution (D. Shimer and G. Chernoff, 9/28/90).

SUMMARY:
By the dermal route, no developmental toxicity was found. Maternal toxicity was observed at 100 mg/kg/day (decreased weight gain) and dermal irritation was seen at all dose levels. Maternal NOEL = 50 mg/kg. Developmental NOEL > 100 mg/kg.

Three oral gavage studies have been reviewed. The first study (001535) used doses which were too high (3-64 mg/kg). A number of the effects were noted in fetuses in the 48 and 64 mg/kg groups which were associated with maternal toxicity. Adverse effects were also seen in the absence of maternal toxicity at dose levels of 3 and 12 mg/kg. At 3 mg/kg and 12 mg/kg, 9% (10/113) and 4.5% (4/89) of the pups, respectively, had neural tube or skull malformations. At 48 and 64 mg/kg respectively, 14/108 and 10/88 fetuses had findings. Hydrocephaly was also observed. The study

concludes that Karathane caused developmental toxicity with no NOEL established. The second study (001539) used lower doses (0.1, 0.5 and 48) and many more rabbits/group. A number of toxic effects were seen at 48 mg/kg including developmental toxicity (resorptions) and a decreased maternal weight gain. For maternal and developmental toxicity the NOEL was determined to be 0.5 mg/kg/day. A re-evaluation of these two studies by J. Parker on 3/31/86 and 6/10/86 concluded that the maternal NOEL is 3.0 mg/kg/day and the developmental NOEL is 0.5 mg/kg/day. Based on this finding of developmental toxicity at a dose level below that for maternal toxicity, considering both studies together, a possible adverse effect was noted, and recommendation forwarded that risk assessment should be performed to determine if an adequate margin of safety exists.

In the final oral study (record no. 071177), a new technical material with a minimum of 92% a.i. was used. The results demonstrated that developmental effects (increased resorptions, decreased fetal weight, vertebral asymmetry) occurred at dose levels higher than those causing maternal toxicity (Developmental NOEL = 12 mg/kg/day vs. Maternal NOEL = 3 mg/kg/day). This finding indicates that with the new technical material, developmental toxicity is secondary to maternal toxicity, and that the developmental effects seen should not be considered an adverse developmental health effect. In conclusion, it appears that the old technical products with less than 84% a.i. are teratogenic in rabbits, and that the new technicals with greater than 92% a.i. are not teratogenic (G. Chernoff, 9/28/90).

TERATOLOGY, OTHER (INCLUDING MOUSE)

030 050479, "Prenatal Exposure to the Fungicide Dinocap Causes Behavioral Torticollis, Ballooning and Cleft Palate in Mice but Not Rats or Hamsters", (Published in Teratogenesis, Carcinogenesis, and Mutagenesis 6:33-43(1986), Health Effects Research Laboratory, Reproductive Toxicology Branch and Perinatal Toxicology Branch, U.S. EPA, and Northrop Services, Inc., Research Triangle Park, NC.). Dinocap technical, Lot# 3-83122, 84% a.i.; administered by gastric intubation to pregnant mice (days 7-16 of gestation) in groups of 30-31 at 0, 6, 12 and 25 mg/kg/day and to a second set of mice in groups of 30, 30 and 40 at 0, 12 and 25 mg/kg/day, respectively; to pregnant rats (days 7-20 of gestation) in groups of 20, 21 and 21at 0, 50 and 100 mg/kg/day, respectively, and to pregnant hamsters (days 8-11 of gestation) with 10/group at 0, 25, 50, 100 and 200 mg/kg/day and in a separate hamster experiment using groups of 8 at 0 and 50 mg/kg/day (administered days 7-14 of gestation). **ADVERSE EFFECTS** in mice, including high neonatal pup mortality, ballooning of gastrointestinal tract associated with cleft palate, reduced body weight at weaning, delayed vaginal opening and behavioral torticollis (a twisting of the neck resulting in tilting of the head) associated with other aberrant behaviors and increased reactive locomotor activity. Doses used in mice not toxic to dams (Maternal NOEL $\geq$ 25 mg/kg; Develop. tox. (pup) NOEL = 6 mg/kg. In the first hamster experiment maternal toxicity in high dose group resulted in 4/10 dams resorbing their litters, also seen in this group was a severe reduction in pup viability (which also occurred in the 100 mg/kg/day group), retarded growth through day 45, necropsy revealed reduced body and organ weights of pups as compared to controls, and the three highest dose groups had reduced pup biomass; in the second hamster experiment, reduced pup biomass was the only effect seen (Maternal NOEL = 50 mg/kg/day (body weight); Develop.tox. NOEL = 50 mg/kg/day). No adverse effects other than maternal toxicity were noted in rats (Maternal NOEL = 50 mg/kg/day (decreased body weight gain); develop. tox. NOEL $\geq$ 100 mg/kg). **UNACCEPTABLE** (published reference, full study protocol(s) and raw data not provided). HGM, 6/30/87 and Gee, 7/17/87.

040 071178, "Developmental Toxicity of Dinocap in the Mouse Is Not Due to Two Isomers of the Major Active Ingredients" (Rogers, J.M., L.E. Gray, B.D. Carver and R.J. Kavlock, Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, Teratogenesis, Carcinogenesis, and Mutagenesis 7:341-346, 1987). This study was conducted in 2 parts. Technical Dinocap (84% a.i.),

2,4-dinitro-6-(1-methylheptyl)phenyl crotonate, the 2,6-isomer, or a 2:1 mixture of 2,4-isomer and 2,6-isomer was administered by gastric intubation to groups of 6-9 CD-1 mice at 25 mg/kg/day on days 7-16 of gestation. Dams were sacrificed on day 18 and fetuses examined for cleft palate. Affected fetuses were observed only in the technical Dinocap group, where the rate was 57%. In the second part of the study, groups of 7-12 dams were dosed in a similar manner, and then allowed to deliver. Pups were observed for 45 days. As in the first part of the study, only the technical Dinocap group exhibited adverse effects. These included a 50% reduction in survival, body weight reduction at day 30 (last time weighed), 60% otolith agenesis, torticollis, and abnormal swimming. The authors conclude that the isomers are not teratogenic, and that another side chain in the active ingredient, or a lesser component is responsible for the teratogenesis. **SUPPLEMENTAL INFORMATION,** not a guideline study (D. Shimer and G. Chernoff, 9/28/90).

040 071179, "Teratogenic Effects of the Fungicide Dinocap in the Mouse", (Rogers, J.M., B. Carver, L.E. Gray, J.A. Gray and R.J. Kavlock, Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, Teratogenesis, Carcinogenesis, and Mutagenesis 6:375-381, 1986). Technical Dinocap, 84%, lot 3-83122, was administered by gavage to CD-1 mice at dose levels of 0, 5, 10, 20, 40, 80 or 120 mg/kg/day on days 7-16 of gestation. Group size varied from 20 at the highest dose to 58 - 88 mice in other groups. At 120 mg/kg/day, there was 80% maternal mortality and no live fetuses. At 80 mg/kg, there was 29% maternal mortality, decreased maternal weight gain, and a reduced number of live fetuses. There was a dose related decrease in fetal weight which was statistically significant at 5 mg/kg. There was a similar dose related increase in cleft palate (0.4, 23.6, 75.5, and 74.1% at 5, 20, 40, and 80 mg/kg/day, respectively). Maternal NOEL = 40 mg/kg; Developmental NOEL < 5 mg/kg. Based on these findings, the authors conclude that Dinocap is teratogenic at doses less than those causing maternal toxicity. **SUPPLEMENTAL INFORMATION**, not a guideline study (D. Shimer and G. Chernoff, 9/28/90).

040 071180, "The Mouse Teratogen Dinocap Has Lower A/D Ratios and Is Not Teratogenic in the Rat and Hamster" (Rogers, J.M., B. Barbee, L.M. Burkhead, E.A. Rushin and R.J. Kavlock, Health Effects Research Laboratory, U.S. EPA,. Research Triangle Park, NC, Teratology 37:553-559, 1988). This study was designed to examine adult to developmental toxicity ratios (A/D) across species. Technical Dinocap, 84%, lot 3-83122, was administered by oral gavage to groups of Sprague-Dawley rats at dose levels of 0, 100, 150 or 200 mg/kg/day on days 7-20 of gestation. Decreases in maternal extrauterine weight and fetal weight at 150 mg/kg resulted in an A/D ratio of 1.0. Administering the test compound to groups of Syrian golden hamsters at dose levels of 0, 12.5, 25, 50, 75, 100 or 200 mg/kg/day on days 7-14 of gestation resulted in decreased maternal and fetal weights at 2.5 mg/kg, and enlarged fetal renal pelvis at 25 mg/kg. The A/D ratio for hamsters was less than 0.5. The authors conclude that the high A/D ratio reported in mice may be due to differences in placental transfer or distribution of a sensitive receptor. **SUPPLEMENTAL INFORMATION**, not a guideline study (D. Shimer and G. Chernoff, 9/28/90).

040 071181, "Prenatal Dinocap Exposure Alters Swimming Behavior in Mice Due to Complete Otolith Agenesis in the Inner Ear", (Gray, L.E., J.M. Rogers, J.S. Ostby, R.J. Kavlock and J.M. Ferrell, Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, Toxicology and Applied Pharmacology 92, 266-273, 1988). Dinocap, 84%, was administered by oral gavage to groups of 57 to 206 pregnant CD-1 mice at dose levels of 0, 6, 12 or 25 mg/kg/day on days 7-16 of gestation. Postnatal behavioral development resulting from agenesis of the otoliths in prenatally exposed animals was assessed at 120 days. Torticollis (head tilting) was observed at 3 weeks of age in 4.4 and 25.3% of the offspring from the 12 and 25 mg/kg/day dose groups, respectively. Swimming was adversely effected in 6.8 and 47.2% of the 12 and 25 mg/kg/day dose groups, respectively. At 12 mg/kg/day, 19% of the offspring were missing one or more whole otoliths. **SUPPLEMENTAL INFORMATION**, not a guideline study (D. Shimer and G. Chernoff, 9/28/90).

GENE MUTATION

015 024858, "Karathane Technical: Microbial Mutagenicity Assay", (Rohm and Haas, 2/22/1985, Report 85R 0039). Salmonella TA1538 and TA98 only. Tested at 0, 20, 200, 500, 2000 and 5000 ug/plate, with and without activation, triplicate plates. Tested 6 lots of Dinocap at 83.9 to > 95% purity. **ADVERSE EFFECT**: 5/6 were mutagenic at 5000 ug/plate in TA1538, especially without S9 activation. **UNACCEPTABLE**, not upgradeable (no repeat trial). Individual plate counts for TA1538 and TA98 for each lot tested are in 029 050475. JR(G), 6/10/85.
EPA 1-liner: Acceptable; positive mutagenic effect in TA-1538 without S9 activation.

007 024891, "Karathane Technical: Microbial Mutagenicity Screen", (Rohm & Haas, 11/20/1984, 84R 0243). Salmonella TA1538 and TA98. 7 lots of Dinocap were tested at 0, 20, 50, 200, 500, 2000 and 5000 ug/plate, with and without activation, 3 plate per concentration. Purity varied from 78.7 to 88.6 %. **UNACCEPTABLE**, not upgradeable (no repeat trial, 2 strains only, missing positive controls without activation). **ADVERSE EFFECT**, marginal response: 5/7 in TA98 +S9 at 5000 (1.6-1.75X); TA1538, 7/7 lots -S9 at 2000 ug (2-3X). Individual plate counts for TA98 and TA1538 for all lots are in 029 050475. JR(G), 6/10/85.
EPA 1-liner: Activated assays - acceptable; nonactivated assays - inconclusive. Equivocal mutagenesis at 5000 ug/plate in TA98; Presumptive positive in TA1538 at 2000 ug/plate.

007 024892, "Microbial Mutagenicity Assay: Karathane Technical", (Rohm & Haas, 10/23/1984, 84R 0203). Salmonella, strains TA1535, TA1537, TA1538, TA98 and TA100. One lot, 2539 at 88.1%. Tested at 0, 50, 200, 500, 2000 4000, 4500, 5000, 5500 and 6000 ug/plate, with and without activation. **UNACCEPTABLE** (high SR values, no -S9 positive controls). **ADVERSE EFFECT**, marginal response in TA98 with activation in presence of precipitate. Individual plate counts for TA98, TA1538,TA100, TA1537 and TA1535 are in 029 050475. JR(G), 6/10/85.
EPA 1-liner: Activated assays - acceptable with a positive response in TA98 at 4000 and 6000 ug/plate. Nonactivated assays - unacceptable [no reason stated].

007 024893, "Karathane Technical: Microbial Mutagen Test", (Rohm & Haas, 10/28/82, 82R 233). Salmonella TA98 and TA1538, 5 lots at 79 - 82 % purity, triplicate plates, 0, 250, 750, 2500, 5000 and 7500 nl/plate, with and without activation. Stated as "insoluble" at ≥ 2500 nl/plate. **UNACCEPTABLE**, not upgradeable (lacks positive controls without activation, no repeat trial). **NO ADVERSE MUTAGENIC EFFECT REPORTED**. Individual plate counts for TA1538 and TA98 - all 5 lots - in 029 050475. JR(G), 6/10/85.
EPA 1-liner: Activated assays - acceptable; Nonactivated assays - unacceptable [no reason stated]; not mutagenic in TA98.

007 024894, "Karathane: Microbial Mutagen Assay", (Rohm& Haas, 7/20/1982,82R-96). Salmonella, 5 strains, TA1535, TA1537, TA1538, TA98 and TA100. Lot 2023, Italy, no purity stated. Tested at 0, 0.001, 0.01. 0.1, 1.0 and 5.0 ul/plate in triplicate, with and without activation. **UNACCEPTABLE** (no repeat trial, no positive controls without activation). **NO ADVERSE MUTAGENIC EFFECT REPORTED**. Individual plate counts for TA1535 in 029 050475. JR(G),6/10/85.
EPA 1-liner: Activated assays - acceptable; nonactivated assays-unacceptable. No positive effect in TA1535, TA1537, TA1538 and TA100.

007 024895, "Karathane Technical: Microbial Mutagen Test", (Rohm & Haas, 8/18/1982, 82R-74). Salmonella, strains TA1535, TA1537, TA1538, TA98 and TA100. Lot 2080, Italy, no purity stated. Tested at 0, 0.001, 0.01, 0.1, 1.0 and 5.0 ul/plate, in triplicate, with and without activation. **UNACCEPTABLE** (repeat trial with TA98 only). **NO ADVERSE EFFECT REPORTED**. Individual plate counts for TA1535 in 029 050475. JR(G), 6/10/85.
EPA 1-liner: Activated assays - inconclusive, not a mutagen in TA1535, TA1537, TA1538 and

TA100; nonactivated assays - unacceptable, no comment.

007 024896, "Karathane Technical (RH-23,004): Microbial Mutagen Test", (Rohm and Haas, 12/6/1981, 81R-290). Salmonella, strains TA1535, TA1537, TA1538, TA98 and TA100, with and without activation, lot 3-7039, 83.7 % purity, triplicate plates, 0.001, 0.01, 0.1, 1.0 and 5 ul/plate. **UNACCEPTABLE** (missing controls for -S9). **NO MUTAGENIC EFFECT REPORTED**, except for TA1538, especially -S9. Multiple trials with inconsistent results. Precipitate at ≥ 1.0 ul/plate. Consider biological significance questionable. Individual plate counts in 029 050475. JR(G), 6/7/85.
EPA 1-liner: Activated assays - acceptable, not a mutagen in TA1535, TA1537, TA1538 and TA98; nonactivated assays - unacceptable; presumptive positive effects for TA1538 (dose levels: 0.5 and 5.0 ul/plate).

007 028978, "Mutagenicity Study of Karathane in Bacteria", (Japan Institute of Environmental Toxicology, 4/2/1979). Salmonella, strains TA1535, TA1537, TA1538, TA98 and TA100. Dinocap, 78% purity, tested at 0, 10, 50, 100, 500, 1000, 2000 and 5000 ug/plate in duplicate, with and without activation. No lot number. **UNACCEPTABLE** (high control counts of over 10,000, no repeat trial). **POSSIBLE MUTAGENIC EFFECT** in TA1538 (2X) and TA98 (2X) without activation. Toxicity at 5000 ug. JR(G), 6/7/85.
EPA 1-liner: Acceptable - positive mutagen in TA98 and TA1538 in the absence of activation.

007 024885, "Karathane (Purified): Microbial Mutagen Test", (Rohm & Haas, 1981, 81R-220). Salmonella, strains TA1535, TA1537, TA1538, TA98 and TA100, #WR 9297-6 (100% purified) tested at 0, 0.001, 0.01, 0.1, 1.0 and 5 ul/plate in triplicate with and without activation. **UNACCEPTABLE** (no individual plate counts, no repeat trial). **NO MUTAGENIC EFFECT REPORTED**. JR(G), 6/7/85.
EPA 1-liner: Activation assays - acceptable, not a mutagen in TA1535, TA1537, TA1538 and TA98; nonactivated assays - unacceptable [no reason stated].

006 024867, "Karathane Mutagenicity: Summary and Evaluation - Gene Mutation using Salmonella typhimurium and Escherichia coli", (Rohm and Haas, 8/1983). Summary and evaluation. Mixed results with more negatives than positives. JR(G), 6/7/85.

007 024890, "Ames Test Results on Karathane Samples". Summary of 1984 Ames testing; **ADVERSE EFFECT** noted in TA98 and TA1538 (the only strains listed.) See 024891, etc. Lists lot numbers, % a. i., % DNOPC and DNOP in each lot. JR(G), 6/10/85.

SUMMARY comments. Although each study was found unacceptable due to flaws in the design or in the reporting of data, CDFA thinks collectively they provide sufficient data. Some reports contain information on precipitation at higher concentrations and this could have confounded colony counts in some of the reports if careful observations were not made. Most reports are so brief that it is not clear whether precipitation was a factor. In addition, the mutagenic response varies with the Lot # so that the effect may be due to a contaminant since the purity of most lots was <90% and occasionally <80%. The combination of all of the above assays in Salmonella establish that Dinocap is a weak mutagen in bacteria. Gee, 7/21/87.

007 024889, "Mutagenicity Evaluation of Karathane TD-80-343 in the Mouse Lymphoma Forward Mutation Assay", (12/1981, Litton Bionetics, 12/1981, LBI Project 20989, Rohm and Haas Report 81RC-150.). Mouse lymphoma L5178Y. Dinocap (83.7%) tested at 0.488 to 30 nl/ml. Lot 3-7039; four hr. treatment, triplicate plates, 4 trials; **NO INCREASE IN MUTATION FREQUENCY. ACCEPTABLE. JR(G), 6/10/85.
EPA 1-liner: Inconclusive with equivocal results due to precipitation occurring at all dosage levels.

[JRG concurs but since precipitation is a problem in this assay and in the Salmonella assays, these tests may not be appropriate to use. This report was judged acceptable on the basis of the conduct.]

029 050476, "Karathane Technical CHO/HGPRT Gene Mutation Assay", (Rohm & Haas Co. Toxicology Dept., 1/7/86, Report No. 85R-204, Protocol No. 85P-190), Karathane technical, 83.9% a.i., TD No. 84-54, Lot No. 2692 dissolved in DMSO; tested without metabolic activation at 0, 3, 5, 6, 7 and 10.0 ug/ml, and with Aroclor 1254-induced rat liver S-9 metabolic activation (1 mg S-9 protein per ml) at 0, 15, 20 or 25 ug/ml (Trial 1); and 0, 12 or 15 ug/ml with 0.3 or 2 mg S9/ml (Trial 2); exposure period, 18-20 hrs for non-activated cultures and approx. 5 hrs. for activated cultures; after exposure period, cells were grown for approx. 8 days to permit expression of the mutation and subsequently cultured for 7 days in 10 uM 6TG to select for HGPRT locus mutants. **NO ADVERSE EFFECT**. No significant increases in the number of mutant colonies were observed for either the activated or nonactivated cultures at any of the concentrations tested. **NOT ACCEPTABLE** (No repeat trial for nonactivated cultures). HGM, 6/16/87 and Gee, 7/16/87.

SUMMARY: Collectively, the two studies in mammalian cells provide data to indicate that Dinocap does not appear to be mutagenic in either cell type.

CHROMOSOME EFFECTS

007 024887, "Karathane: Micronucleus Test in Mice", (Inst. Environ. Tox., Japan, 1/10/83.). Dinocap (79.4%), Lot 3-62112 tested in a micronucleus test in BDF1 mice at 10.8, 31.5, 43 or 86 mg/kg in a single dose by oral gavage to males and at 11.9, 23.8, 47.5 or 95 mg/kg to females; 3/sex/group. In multiple dosing on 4 consecutive days, males were given 43 mg/kg and females, 23.8 or 47.5 mg/kg with 8/sex. **NO ADVERSE EFFECTS REPORTED. ACCEPTABLE. JR(G), 6/10/85.
Presumed EPA 1-liner (R&H, #83R-16): Acceptable with no mutagenic effect in both sexes using single or repeated administration.

007 024888, "Primary Evaluation of the Cytogenetic Activity and Potential Mutagenic Risk of Twenty-two Pesticides", (1980, publ. in Tsitologiya i Genetika 14: 41-47 (1980).) Twenty-two pesticides were tested in mice with 600 metaphases examined. Mice were given 0, 5, 12.5 or 25 mg/kg by intragastric intubation. Sacrificed at 20 hours. **UNACCEPTABLE** (no justification of dose, no information on toxicity, no individual data, others.) **NO ADVERSE EFFECT REPORTED.** JR(G), 6/10/85.

029 050477, "Clastogenic Evaluation of Karathane Technical", TD# 85-054, Lot# 2692, R & H Protocol No. 84P-590, In An In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies In Chinese Hamster Ovary (CHO) Cells"; (Litton Bionetics, Inc., LBI project No. 20990, 1/86; R & H Report No. 85 RC-62); Karathane Technical, TD#85-054, Lot# 2692 (83.9%); duplicate cultures tested at 0, 5.0, 10.0, 15.0 and 20.0 ug/ml with S-9 (Aroclor 1254 induced rat-liver S-9 activation) and at 0, 1.0, 2.5, 5.0, 7.5, and 10.0 ug/ml without S-9; Range-finding studies: activated cultures exposed for two hours; nonactivated cultures were exposed for 2 hours in presence of test article alone, then 23 hrs in presence of test article and BrdUrd (final concentration = 10 uM). Chromosomal aberration assays: activated and nonactivated cultures were exposed for 2 hours and 7.5 hours, respectively and harvested at 10 hours. **NO ADVERSE EFFECT. ACCEPTABLE. HGM, 6/25/87 and Gee, 7/17/87.

**029 050478, "Karathane In Vivo Cytogenetic Study in Mice", (Rohm and Haas Toxicology Dept., 1/24/86, Protocol No. 84P-571R; Report No. 85R-235). Karathane TD 85-54, 83.9% a.i., Lot No. 2692 diluted with corn oil; single oral dose administered to 30 CD-1 male mice/group at 0

(corn oil vehicle), 15, 75, or 150 mg/kg (0, 12.6, 62.9, or 125.8 mg ai/kg, respectively); 10 animals/group sacrificed and bone marrow slides prepared 6, 28 and 52 hours after dosing; positive control group received 0.3 mg/kg triethylene melamine ip, then 28 hours later were sacrificed and bone marrow slides prepared. Use of males only is justified in Appendix I. **NO ADVERSE EFFECT.** No significant increase in chromosomal aberrations was observed in high dose group as compared to vehicle control group. **ACCEPTABLE**. HGM, 6/25/87 and Gee, 7/17/87.

DNA DAMAGE

007 028977, "Mutagenicity Study of Karathane in Bacteria ", (Japan Institute of Environmental Toxicology, 4/2/1979). Bacillus subtilis rec assay with M45 and H17 strains at 0, 20, 100, 200, 500, 1000 and 2000 ug/disk. Dinocap (78%). **UNACCEPTABLE**, not upgradeable (single plates, no activation only). Some cytotoxicity at higher concentrations in both strains. **NO ADVERSE EFFECT ON GROWTH REPORTED**. JR(G), 6/7/85.
EPA 1-liner: Acceptable, not a mutagen at dose levels from 20 to 2000 ug/disk in a nonactivated assay.

015 024859, "Karathane Technical in vitro Unscheduled DNA Synthesis Assay", (2/22/1985, Rohm & Haas, 85R-003). Dinocap technical, 87.2%. Unscheduled DNA synthesis in rat hepatocytes at 0, 0.25, 0.1, 0.05 and 0.025 ug/ml, tested to toxic levels. Lot 2553. Initially judged unacceptable because of no repeat trial and some viability problems. Reevaluation in response to the rebuttal in 029 upgrades this to **ACCEPTABLE to fill the 844 data gap. **NO ADVERSE EFFECT WAS REPORTED** on DNA repair. Gee, 6/11/85 and 7/21/87.
EPA 1-LINER: Inconclusive, not a mutagen at levels between 0.025 and 0.25 mg/ml. However, no cytotoxicity was shown at the highest dose level.
[Text states that at 0.5 mg/ml, the cells were stripped from the coverslips.]

NEUROTOXICITY

Not required at this time.